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Original Article

Neuromuscular Functions on Experimental Acute Methanol Intoxication

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Abstract

Objective: The incidence of accidental or suicidal ingestion of methyl alcohol is high and methyl alcohol intoxication has high mortality. Methyl alcohol intoxication causes severe neurological sequelae and appears to be a significant problem. Methyl alcohol causes acute metabolic acidosis, optic neuropathy leading to permanent blindness, respiratory failure, circulatory failure and death. It is metabolised in the liver, and its metabolite formic acid has direct toxic effects, causing oxidative stress, mitochondrial damage and increased lipid peroxidation associated with the mechanism of neurotoxicity. Methanol is known to cause acute toxicity of the central nervous system; however, the effects on peripheral neuromuscular transmission are unknown. In our study, we aimed to investigate the electrophysiological effects of experimentally induced acute methanol intoxication on neuromuscular transmission in the early period (first 24 h).

Methods: After approval by the Animal Experiment Ethics Committee of Ege University, the study was carried out on 10 Wistar rats, each weighing about 200 g. During electrophysiological recordings and orogastric tube insertion, the rats were anaesthetised using intra-peritoneal (IP) injection of ketamine 100 mg kg^{-1} and IP injection of xylazine 10 mg kg^{-1}. The rats were given 3 g kg^{-1} methyl alcohol by the orogastric tube. Electrophysiological measurements from the gastrocnemius muscle were compared with baseline.

Results: Latency measurements before and 24 h after methanol injection were 0.81±0.11 ms and 0.76±0.12 ms, respectively. CMAP amplitude measurements before and 24 h after methanol injection were 9.85±0.98 mV and 9.99±0.40 mV, respectively. CMAP duration measurements before and 24 h after methanol injection were 9.86±0.03 ms and 9.86±0.045 ms, respectively.

Conclusion: It was concluded that experimental methanol intoxication in the acute phase (first 24 h) did not affect neuromuscular function.

Keywords: Methanol, intoxication, polyneuropathy, neuromuscular transmission

Introduction

Currently, methyl alcohol intoxications developing by accident or due to a suicide attempt are an important social issue because of high mortality rates and severe late neurological sequelae. Methanol is the first product of alcohol series, and it is used as a solvent or cleaning agent in the industry. It has been reported that the risk of exposure can increase because of its use in industrial products and its suggested use as an alternative automotive fuel (1).

Although permanent blindness and other neurological sequelae associated with optic nerve injury can be observed in cases not resulting in death in the acute period, particularly due to neurotoxic effects, no definite evidence is available related to the development of peripheral neuropathy because most of the patients are unconscious, supported by a mechanical ventilator in the intensive care units and given muscle relaxants and sedative agents when necessary. However, it is known that neuropathies develop clinically in the findings of physical examinations performed in the late period. The effects of methanol, which is accepted as a neurotoxic agent, on the peripheral nervous system in the acute period are unknown.

On the other hand, late admission to the hospital increases mortality and morbidity rates in poisoning cases (2). It is thought that early diagnosis and treatment play an important role in the prevention of mortality and neurological sequelae.

Therefore, in our study, it was aimed to electrophysiologically investigate early peripheral neuromuscular transmission functions (in the first 24 h) in the experimentally designed acute methanol intoxication model.

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Methods

The study started after receiving approval from the Ethics Committee for Animal Experiments in Ege University, and it was conducted in the Department of Anaesthesiology and Reanimation in Faculty of Medicine, Ege University. Before and during the study, the rats were observed and maintained in an air-conditioned environment at a stable room temperature by feeding adequate food and water and by providing a physiological day/night cycle. The study was conducted on five male and five female adult Wistar rats, which weighed approximately 200 g. All of the rats were obtained from the Experimental Surgery Animal Breeding Center in Ege University. During electrophysiological measurements, intraperitoneal (IP) 100 mg kg^{-1} ketamine and IP 10 mg kg^{-1} xylazine were used for anaesthesia.

After obtaining electrophysiological measurement records from the gastrocnemius muscle by the Biopac Student Lab Pro. programme (BIOPAC Data MP35 Acquisition System, BIOPAC Systems, Inc. Santa Barbara, USA) and Stimulator (Stimulator: SS2L Electrode and BSLSTMA Trigger BIOPAC System, Inc. Santa Barbara, USA), 3 g kg^{-1} methanol was administered through a nasogastric catheter. Because the minimum lethal dose is 9.5 g kg^{-1} for rats, the dose of 3 g kg^{-1} (non-lethal) was administered in our study. Twenty-four hours after administering methanol, electrophysiological measurement recordings were obtained again from the same muscle under ketamine/xylazine anaesthetic administration (Figure 1, 2, 3).

Electrophysiological measurements

The left sciatic nerves of the rats, which were under anaesthesia, were stimulated from the sciatic notch with supramaximal stimulus (intensity 10 V, duration 0.1 ms, frequency 1 Hz). HSTM01 superficial disk electrodes (BIOPAC System, Inc. Santa Barbara, USA) were used for electrical stimulation. The compound muscle action potential (CMAP) of the gastrocnemius muscle was monitorized (Figures 1, 2, 3).

The latency and amplitude of CMAP and total duration were calculated with Biopac Student Lab Pro. programme by monitoring in digital media (Figure 3). For each rat, five CMAP waves were recorded and averaged.

Statistical analysis

The baseline CMAP values and changes in the 12th hour values (latency, amplitude and duration), which were calculated using digital recordings (Figure 3), were evaluated for each rat in the Department of Biostatistics and Medical Informatics in Ege University Faculty of Medicine. Non-parametric Wilcoxon signed-rank test was used for statistical analysis, and the values of $p<0.05$ were accepted to be statistically significant.

When the rats died during the study, they were transferred to the Unit of Medical Waste in Ege University Faculty of Medicine. All the rats that survived after the study were also transferred to the Experimental Surgery and Research Laboratory in Ege University for their use as experimental animals in education on interventions such as the establishment of vascular access and insertion of a nasogastric catheter during surgical courses.

Results

After methanol was administered, one rat died in 24 h. Although the baseline CMAP latency value was 0.81±0.11 ms before administering methanol, it was 0.76±0.12 ms in the measurement performed 24 h after administering methanol. Comapred with the baseline value, this change was found to be statistically insignificant (Table 1).

The baseline CMAP amplitude value was 9.85±0.9 mV before the administration of methanol, but it was 9.99±0.40 mV 24 h after administering methanol. This change was statistically insignificant (Table 1).

Before administering methanol, the baseline duration was 9.86±0.03 ms. In the measurement conducted 24 h after methanol administration, the CMAP duration was 9.86±0.04 ms; this change was found to be statistically insignificant (Table 1).

Discussion

Methanol is metabolized first into formaldehyde and then into formic acid by alcohol dehydrogenase and formaldehyde dehydrogenase. Formic acid inhibits cytochrome c oxidase activity. The inhibition of cytochrome c oxidase leads to serious metabolic acidosis. Formic acid with metabolites is a neurotoxic substance. It causes permanent blindness, particularly because of its affinity to the optic nerve. It also leads to depression in the central nervous system, systemic metabolic acidosis, coma and death.

It is also known that, although rare, the administration of methanol can cause neurological symptoms as a late com-

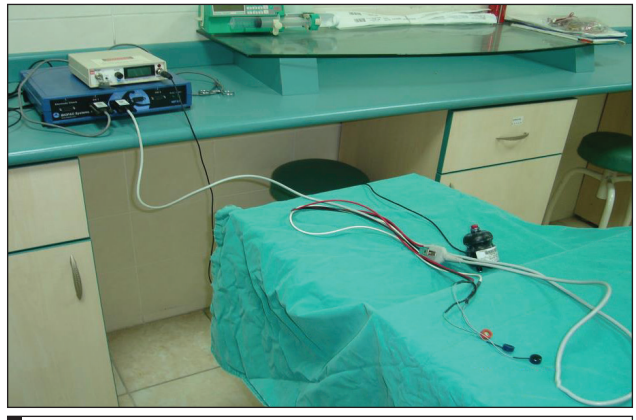

Figure 1. BIOPAC MP35 Data Acquisition System (BIOPAC Systems, Inc., Santabarbara, CA, USA), BSLSTMB Stimulator (BIOPAC Systems, Inc., Santabarbara, CA, USA), BIOPAC HSTM01 superficial stimulation electrodes (BIOPAC Systems, Inc., Santabarbara, CA, USA)

plication as well as acute findings. In a study conducted in 2010, it was reported that methanol application could result in Parkinsonism and polyneuropathy in the late period (3).

Early involvement of the nervous system occurs in the central nervous system, particularly in the optic nerve. Central nerve system involvements are defined as toxic encephalopathy, bilateral putaminal necrosis-haemorrhage, cerebellar and hypothalamic focal lesions, demyelization in subcortical white matter, apoptosis in neuronal and glial cells, cognitive functioning disorders progressing with learning and memory disorders, vertigo, convulsion, loss of consciousness and death. In the late period, permanent neurological sequelae, including polyneuropathies, ataxic gait, Romberg positivity, loss of sense and apraxia in the distal lower extremities and impaired chewing and swallowing functions are observed.

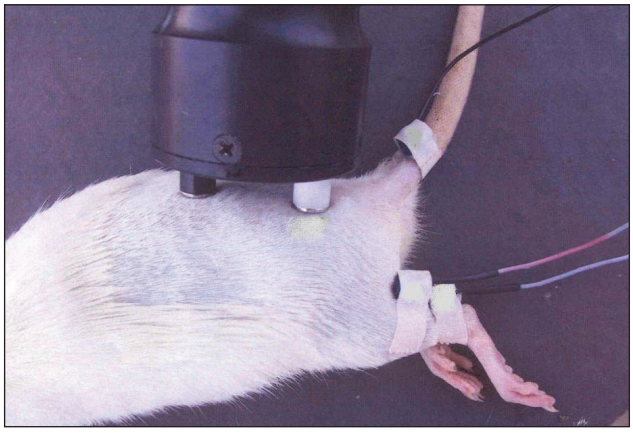

Figure 2. Recording the compound muscle action potential (CMAP) from the *M. Gastrocnemius*

However, no definite data are available on the early development of polyneuropathy.

It is seen that most of the existing experimental models are the studies in which various treatment methods such as biochemical, immunological and histological techniques and different antidote or antioxidant methods are evaluated. Therefore, our study, which aimed to investigate early peripheral neuromuscular transmission functions (in the first 24 h) in the experimentally designed acute methanol intoxication model, included differences compared with other studies in the literature.

Although the minimal lethal dose of methanol was not yet defined in humans in 1950s, Roe et al. (4) reported in the same period that if an exposed individual was not treated and given ethanol, approximately 1 g kg^{-1} methanol could cause death. The half-life of methanol ($t_{1/2}$) varies from 2 h to 24 h. Its lethal oral dose is approximately (30–240 mL) 20–150 g. The minimum accepted toxic dose is 100 mg kg^{-1}.

Table 1. Gastrocnemius compound muscle action potential measurements

	Pre-methanol 0th hour Mean±SD (n=10)	Post-methanol 24th hour Mean±SD
CMAP latency (ms)	0.81±0.11	0.76±0.12
CMAP amplitude (mV)	9.85±0.9	9.99±0.40
CMAP duration (ms)	9.86±0.03	9.86±0.04

ms: milliseconds; mV: millivolt; SD: standard deviation; CMAP: compound muscle action potential

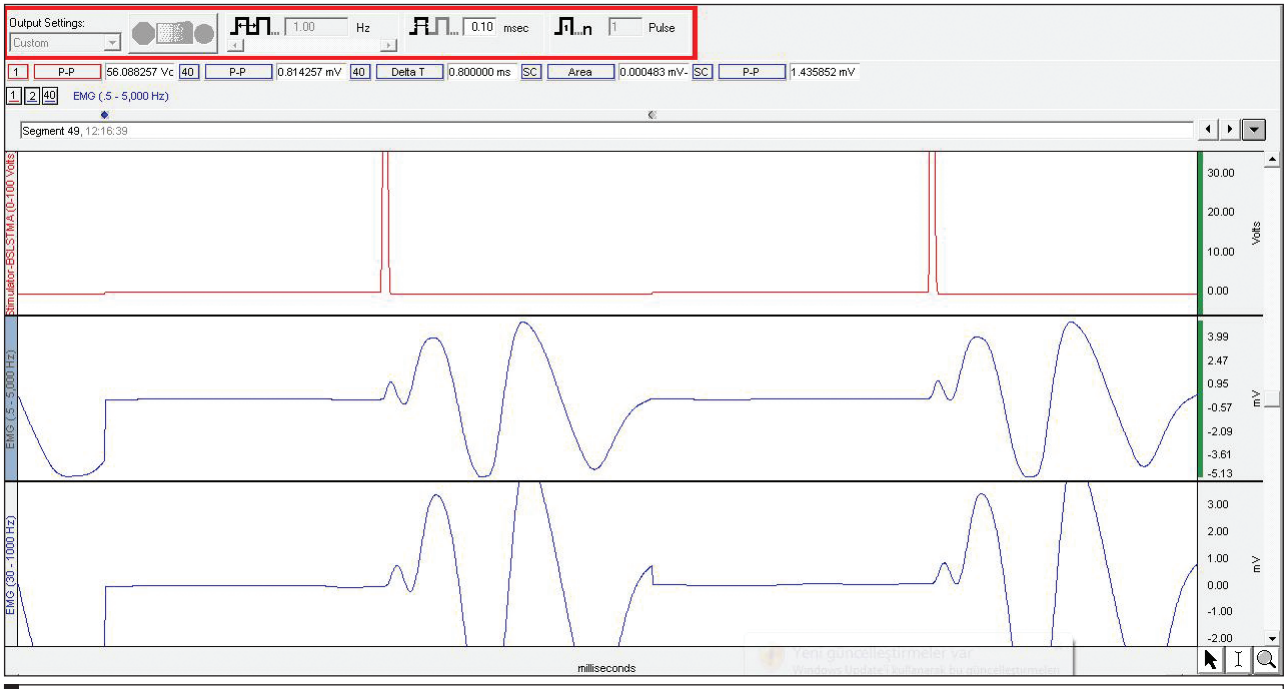

Figure 3. Digital media image in which the measurements of latency, amplitude and duration values were calculated through Biopac BSL Pro version: 3.6.7 programme (BIOPAC Systems, Inc., Santa Barbara, CA, USA)

Although only 3% of ingested methanol is excreted by urine without changing, less than 10% is eliminated from the body through respiration (5). It is known that because methanol is rapidly transformed into formic acid after the latent period, low concentrations of methanol in blood or non-detection of methanol in blood in methanol intoxications can rule out the diagnosis of severe methanol intoxication in patients with clinical signs and findings (5). In some studies in the literature, there are some cases that were diagnosed as methanol intoxication but did not include methanol in blood. Therefore, electrophysiological evaluation is important for early diagnosis as well as further examinations. Different cases for which radiological and electrophysiological examinations were used and recommended for the final diagnosis because methanol could not be detected in blood despite its intake were discussed in the literature (6). In the blood and urine examinations of a patient with a history of alcohol abuse and pre-diagnosis of methanol intoxication, ethyl and methyl alcohol was not found, but electrophysiological examinations were performed for differential diagnosis because of progression with total vision loss and transverse damage in the spinal cord, and the findings of axonal demyelinating polyneuropathy were detected in electromyography (EMG). Therefore, it is specified that the use of radiological and electrophysiological examinations in the acute and chronic periods can be helpful in the diagnosis of methanol intoxication. Contrary to this study, no electrophysiological change was found in our study. However, it is known that the findings of methanol intoxication can also differ according to the dose, intake time and time of intervention.

The nervous system involvements, including Wernicke–Korsakoff syndrome and polyneuropathies, are often encountered with continuous excessive ethyl alcohol intake (alcohol addiction) and accompanying malnutrition (7). Alcohol poisoning cases having alcohol addiction in their anamneses are under greater risk because of malnutrition and vitamin B deficiency. Therefore, because the possibility of polyneuropathy is higher in methyl alcohol intoxication, early diagnosis and treatment are necessary. Methanol intoxication, which mostly develops with chronic alcohol use, increases the oxidative stress with lipid peroxidation impairment in addition to vitamin B deficiency and direct toxic effect on the nervous system. It also causes cytochrome c oxidase inhibition, an increase in lipid peroxidation, inhibition of mitochondrial electron transport chain and a decrease in ATP production necessary for aerobic metabolism and an increase in free oxygen radicals (ROS increase) (8-10). It has been reported that increased free oxygen radicals and mitochondrial injury cause damage, particularly in the liver cells (11-13). It is also suggested that they lead to impairment in the hypothalamic-pituitary axis functions as a result of oxidative stress induced by methanol and in specific and non-specific immune responses by changing the level of corticosterone (8). An increase in improved lipid peroxidation and free oxygen radicals causes damage in the hypothalamus-pituitary-adrenal pathway and in the sympathetic nervous system, providing innervations of lymphoid tissues. Parthasarathy et al. (8) suggest that when the hypothalamus-pituitary-adrenal pathway is affected by oxidative stress because of methanol intoxication, corticosterone level decreases; thus, impaired specific and non-specific immune responses occur.

Because the primary aim of our study was to investigate neuromuscular conduction in the acute period of methanol intoxication, any parameter for its increasing oxidative stress was not examined. We suggest that differently designed future studies on the ability of methyl alcohol to trigger oxidative stress by causing increased lipid peroxidation are needed.

Toxic effects on the nervous system and nervous system involvements in the acute and chronic periods are accepted as specific findings of methanol intoxications. The occurrence of the central nervous system and peripheral nervous system involvements have been demonstrated in various studies and case reports through clinical, morphological, electrophysiological and imaging techniques. In autopsy examinations performed on cases who died because of methanol intoxication, it was reported that cerebral oedema, occipital, temporal and parietal cortex; petechial haemorrhage in the basal ganglion and pons; haemorrhagic necrosis in the putamen and thalamus and haemorrhagic leukoencephalopathy were observed as the nervous system involvements (14, 15).

It is seen that most of the existent studies on methanol are about the serious effect of metabolic acidosis and formic acid formation on prognosis and mortality, with the development of optic neuropathy/vision loss. Optic neuropathy and putaminal necrosis are known to be the most common sequelae. However, Gille et al. (16) presented a case that developed chronic motor neuropathy with polyneuropathy involving the peripheral nervous system in addition to known neurological sequelae in 1998. The main complications of methanol intoxication are optic neuropathy, putaminal necrosis and metabolic acidosis. Bilateral vision loss can be permanent in surviving patients. It is reported that Parkinson-like findings, polyneuropathy and rare occurrences of apraxia in the extremities can be observed (17-19). Quartarone et al. (19) studied a patient with chewing dysfunction progressing with drinking and swallowing disorder in addition to bilateral blindness and Parkinson-like findings. In the cranial tomography performed in the acute period after oral methanol intake (2 days after), hypodense areas were observed in the putaminal nucleus. In the cranial magnetic resonance imaging performed for further examination, the existence of hypodense areas in the caudate nucleus and putamen was confirmed. No damage was observed in the brain stem and cortical region. Fundoscopy of the patient with bilateral vision loss was performed a few weeks later, and the patient was diagnosed with optic atrophy. In the neurological examination performed because of the incidence of speaking and chewing disorders approximately a year later, bilateral vision loss, dysarthria, gait im-

pairment, loss of distal tendon reflexes, dysesthesia in the feet and limitation of the jaw motions were observed. It was specified that transcranial magnetic stimulation results of the cranial nerves (5th and 7th cranial nerves) and the corticobulbar tract were normal, but mild polyneuropathy findings were revealed in the electromyographic evaluation. The case presented has the features of masticatory muscles dysfunction and polyneuropathy findings in the electromyographic examinations in addition to the known classical findings seen after methanol intoxication (19). It is seen in this clinical case that electrophysiological examination was performed for diagnosis after the occurrence of clinical findings with dysfunction of the masticatory muscles and 1 year later in the late period.

Another case report in the literature is about a 34-year-old patient who consumed methanol and other solvents accidentally. Motor neuron disorder, similar to amyotrophic lateral sclerosis, was reported after intoxication. It was specified that the onset of clinical symptoms was within the bounds of biological possibility. Considering the patient's age, familial history and absence of neurological disorders, the possibility of the development after intoxication was evaluated (20).

Jarwani et al. (21) reported a 26-year-old patient who had central nervous system and peripheral nervous system involvements together. In the patient with bilateral optic neuropathy, radiculopathy and polyneuropathy accompanied by axonopathy developed. Magnetic resonance imaging of the central nervous system revealed necrosis in the putamen. Muscle strength was reported to be 4/5 in the upper extremities and 3/5 in the lower extremities. In early electrophysiological examinations (EMG and nerve conduction velocity), sensory and motor polyneuropathy accompanied by secondary axonopathy and early polyradiculopathy, particularly in the lower extremities, were detected. It was stated that no improvement was seen in sensory and motor functions despite supportive therapy, corticosteroid therapy and folic acid therapy. It was reported that the pathogenesis of polyradiculopathy that developed could not be accurately explained (21). This case is included in the literature as a remarkable study because of the presence of both central and peripheral system involvements. It is suggested that one should consider that polyneuropathies can be observed as sequelae with bilateral putaminal necrosis in methanol intoxications (21). It was discussed that polyneuropathy developed in this study was similar to polyneuropathy in ethylene glycol intoxication, but there was no information on ethylene glycol intake in the medical history of patient. On the other hand, considering the time of admission to the hospital, it is seen that the patient did not come to the hospital within the first 24 h and was admitted 24 h after methyl alcohol intake. Contrary to this case in which polyneuropathy was detected in electrophysiological examinations, no change was observed in neuromuscular functions in the acute period in our electrophysiological evaluation performed in the early period of methanol intoxication as a result of latency, amplitude and duration calculations obtained from the measurements of CMAPs from the *M. Gastrocnemius*. No finding showing the development of polyneuropathy was encountered. However, it should be considered that the exposed concentration of methyl alcohol, whether any treatment has been applied or not and the time when electrophysiological measurements have been performed can affect the results. On the other hand, it is remarkable that electrophysiological examinations, which showed the presence of axonopathy findings in the lower extremities, were performed after the clinical detection of polyneuropathy. Based on this point, it must be interpreted differently from our study because our aim in the experimental model was to electrophysiologically investigate the presence of polyneuropathy without clinical findings after 24 h. Because EMG results were not shared in this case report, in which secondary axonopathy and polyneuropathy were presented, it could not be compared with the data in our study.

Moreover, it has been reported that central nervous system injury, Parkinson-like findings and axonal and sensorial polyneuropathies, particularly in the lower extremities, can develop in individuals who are exposed to solvents, including manganese, carbonmonoxyde and methanol, for a long time because of their occupations. Electrophysiological examinations are also included among diagnostic techniques used for people exposed to solvents for a long time (22). Electromyographic examinations, which supported the existence of polyneuropathy in developing clinical findings, are performed in the late period, differently from our study.

In early electrophysiological examinations performed in the first 48 h for 19 patients admitted to the hospital with the diagnosis of methanol intoxication, retinal dysfunction and optic neuropathy findings were detected (23). Although this study was similar to ours with respect to the early use of the electrophysiological examination, it is seen that the electrophysiological examination included only visual evoked potentials. On the other hand, different from our study, any electrophysiological examination for peripheral nerve involvement was also not mentioned in this study.

Similar to our study, based on the electrophysiological measurements performed in the diaphragms of rats, it is suggested that methanol, which is formed experimentally, alter the neuromuscular junction activity of short-chain aliphatic alcohols (24). As is known, methyl alcohol is included in the monoalcohols class among the aliphatic alcohols.

Our study, which was conducted on the hypothesis that the electrophysiological detection of neuropathies that could develop in the early period was important for the early determination of late neurological sequelae and for taking necessary precautions, is different from other case reports and clinical research in the literature. It is seen in the literature that most of the studies in which EMG was performed are clinical studies conducted in the late period (after the onset of symptoms). In most of the similar studies, electrophysiological examina-

tions have been performed for diagnosis and confirmation in the presence of symptoms and after the clinical detection of polyneuropathy. It is seen that in early electrophysiological studies, only evoked potentials of the optic nerve were evaluated or the values of neuromuscular conduction (CMAP values) were not clearly given, as in our study, and they were the cases accompanied by clinical findings. Based on the case reports in the literature, it is seen that methyl alcohol, which causes cause late peripheral polyneuropathy, can also lead to early polyneuropathy. However, in our study, in our electrophysiological examination conducted in the early period of experimental methanol intoxication, no change was observed in neuromuscular functions in the acute period as a result of latency, duration and amplitude calculations obtained from the measurements of CMAPs from the *M. Gastrocnemius*. On the other hand, we think that the dose of methyl alcohol and action time can be effective on this result; therefore, further studies should be conducted with new experimental methyl alcohol intoxication models regulated with different doses.

Based on the existent studies on methanol intoxication, it is believed that our study, in which peripheral neuromuscular conduction in the acute phase was electrophysiologically investigated, has contributed to the literature as an experimental model.

Conclusion

In our study, which aimed to investigate early peripheral neuromuscular transmission functions (in the first 24 h) in the experimentally designed acute methanol intoxication model, no electrophysiological change was observed in neuromuscular conduction functions during the acute period (in the first 24 h) of experimental methanol intoxication.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ege University Animal Experiments Local Ethics.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.R.M., İ.Ç., D.S., Ö.B.; Design - A.R.M., İ.Ç., D.S., Ö.B.; Supervision - A.R.M., İ.Ç., D.S., Ö.B.; Funding - A.R.M., İ.Ç., D.S., Ö.B.; Materials - A.R.M., İ.Ç., D.S., Ö.B.; Data Collection and/or Processing - A.R.M., İ.Ç., D.S., Ö.B.; Analysis and/or Interpretation - A.R.M., İ.Ç., D.S., Ö.B.; Literature Review - A.R.M., İ.Ç., D.S., Ö.B.; Writer - A.R.M., İ.Ç., D.S., Ö.B.; Critical Review - A.R.M., İ.Ç.; Other - A.R.M., İ.Ç.

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